Cost-Effectiveness of Eltrombopag versus Romiplostim for the Treatment of Chronic Immune Thrombocytopenia in England and Wales

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ABSTRACT

Objective: To evaluate the cost-effectiveness of eltrombopag compared with romiplostim as a treatment for chronic immune thrombocytopenia (cITP) in patients who are splenectomized or ineligible for splenectomy and are treatment refractory in England and Wales.

Methods: A Markov cohort model in which patients were administered a sequence of treatments was used to predict long-term outcomes associated with each treatment. The model was informed by data from the eltrombopag clinical trial program and the available literature. The analysis was conducted from the perspective of the United Kingdom National Health Service, and a lifetime time horizon was used. Deterministic and probabilistic sensitivity analyses were performed.

Results: Eltrombopag dominated romiplostim (i.e., eltrombopag was as effective as but less costly than romiplostim) in both splenectomized and non-splenectomized patients, assuming a class effect for the two treatments. Eltrombopag also dominated romiplostim in the majority of deterministic sensitivity analyses with the exception of when indirect efficacy estimates were incorporated into the model. In this analysis, eltrombopag no longer dominated romiplostim but remained cost-effective versus romiplostim at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year (QALY). Probabilistic sensitivity analysis demonstrated that there was a 99% and 92% chance of eltrombopag being cost-effective at a cost-effectiveness threshold of £20,000/QALY in splenectomized and non-splenectomized patients, respectively.

Conclusions: Results of this study demonstrate that eltrombopag is cost-effective when compared to romiplostim as a treatment for cITP, representing good value for the United Kingdom National Health Service.

INTRODUCTION

Primary immune thrombocytopenia (ITP) is a disease involving increased platelet destruction and impaired platelet production, leading to low platelet counts and impaired blood clotting (1, 2). The prevalence of ITP in the United Kingdom (UK) is 0.05% (3). Bleeding symptoms range from mild bruising to serious, potentially fatal, hemorrhage. Patients with ITP lasting >12 months are considered to have chronic ITP (cITP) (2). Patients with cITP are often unresponsive to one or more agents, and their disease is associated with significant morbidity, impaired quality of life, and increased mortality (4, 5). The goals of treatment are to reduce the risk of bleeding by elevating platelet counts while minimizing treatment-related side effects (2).

The management of ITP is complex (6). Following first-line treatment with corticosteroids or immunoglobulins (Ig), there is no clearly defined treatment pathway, and evidence from randomized controlled trials is scarce (6). Management of ITP is generally tailored to the individual patient depending on their symptoms, platelet count, lifestyle, and adverse events (AEs) associated with different therapies. Splenectomy is a potentially curative treatment option for cITP but is invasive, irreversible, and not appropriate for all patients (6). Patients typically cycle through several treatment options with differing lengths of response, some of which have significant side effects and most of which are not licensed treatments for ITP (6). Rescue treatments such as intravenous (IV) corticosteroids or IVIg may be given when a patient bleeds or is considered at high risk of bleeding (7). These are used either as an adjunct to the patient's primary therapy or once non-rescue treatment options have been exhausted.

Eltrombopag is an oral thrombopoietin receptor agonist (TPO-RA) that stimulates the proliferation and differentiation of megakaryocytes in the bone marrow, resulting in a dose-dependent increase in normal-functioning platelet levels (8-10). Eltrombopag is licensed in the European Union (EU) for treatment of adult splenectomized patients with cITP who are refractory to other treatments and may also be considered as second-line treatment for adult non-splenectomized cITP patients where splenectomy is contraindicated (11).

In the phase 3 registration trial (Randomized Placebo-Controlled Idiopathic Thrombocytopenic Purpura Study With Eltrombopag [RAISE]; ClinicalTrials.gov identifier: NCT00370331) comparing eltrombopag to placebo, eltrombopag produced clinically meaningful and statistically significant differences versus placebo as an addition to standard of care, achieiving the primary endpoint (odds of achieving a platelet count between 50–400×10^9/L) and prespecified bleeding endpoints (12). Furthermore, eltrombopag allowed patients to reduce their use of concomitant and rescue medications. An ongoing long-term extension study (Eltrombopag Extended Dosing Study [EXTEND]; NCT00351468), where some patients have now been followed for >5 years, confirms the long-term efficacy of eltrombopag in cITP and showed that eltrombopag is generally well tolerated (13, 14).

Romiplostim, a peptibody TPO-RA that mimics thrombopoietin, is administered by weekly subcutaneous injection and was approved in the EU in 2009. Like eltrombopag, the studies leading to its approval were randomized controlled trials versus placebo or standard of care (15-17). In two parallel phase 3 studies of splenectomized or non-splenectomized patients, 83% of the combined study populations achieved a durable platelet response, which was defined as ≥4 weekly platelet responses at any time during the study. Romiplostim and eltrombopag are licensed for identical populations by the European Medicines Agency (11, 18).

Using available clinical data and the existing literature, an economic evaluation was designed to assess the cost-effectiveness of eltrombopag versus romiplostim among patients with cITP who previously underwent treatment with azathioprine, mycophenolate mofetil, cyclosporine, dapsone, danazol, cyclophosphamide, vincristine, and/or vinblastine (19, 20). Patients at a high risk of bleeding or who require frequent rescue therapy were modelled. Romiplostim is recommended by National Institute for Health and Care Excellence (NICE) and considered the standard of care amongst the patient group evaluated in this cost-effectiveness analysis. The model underpinning the current analysis informed the NICE appraisal of eltrombopag.

METHODS

This de novo economic evaluation was designed to assess the cost-effectiveness of treatment with eltrombopag compared with romiplostim in two patient populations: (1) adult splenectomized cITP patients who are refractory to other treatments (e.g., corticosteroids, IVIg) and (2) adult non-splenectomized cITP patients who are refractory to other treatments (e.g., corticosteroids, IVIg) and in whom splenectomy is contraindicated. Previous interventions in these patients included corticosteroids, which were the most frequently reported prior treatment in RAISE, immunoglobulins, splenectomy, rituximab, cyclophosphamide, and romiplostim. The total number of previous treatments for cITP administered to study participants is shown in Table 1 (12). These patient groups are within the marketing authorizations in the EU for both TPO-RAs. Additionally, these patients are within those included in the RAISE trial. The current evaluation intends to represent the experience of those patients at a high risk of bleeding who required frequent rescue therapy.

The model assumed that patients receive a series of cITP treatments following their treatment with eltrombopag or romiplostim. This treatment sequence consisted of azathioprine, mycophenolate mofetil, cyclosporine, dapsone, danazol, cyclophosphamide, vincristine, and vinblastine. If a patient fails the current treatment, he or she is moved to the next treatment in the sequence. Patients were assumed to have a specific probability of receiving each treatment in the pathway (Supplemental Material). These probabilities were derived from a physician survey conducted by the romiplostim manufacturer and taken from the manufacturer's submission for the NICE appraisal of romiplostim (21). Rituximab was not included in the base-case treatment sequence because it would predominantly be used prior to a TPO-RA (19).

A Markov cohort model was used to estimate the time spent in each of six health states for each treatment: a long-term responder state (platelets $\geq 50\times10^9$/L), a long-term non-responder state (platelets $<50\times10^9$/L), and four non-responder tunnel states of 4-week intervals that were used to model a patient's time to response (Fig. 1). Transition between health states was dependent on response rate, time taken to respond, and duration of response for each treatment. Within each health state, patients faced a risk of experiencing an outpatient or inpatient bleed and an independent risk of requiring rescue treatment (IVIg, anti-D, IV corticosteroids, or platelet transfusion). Patients within the non-responder health state were

assumed to start a new treatment if they experienced a bleed or failed rescue treatment. Once all treatment options along the pathway had been exhausted, patients were assumed to remain in the long-term non-responder state. Patients could die from general or ITP-related causes from any health state.

The analysis was conducted from the perspective of the UK National Health Service (NHS) in England and Wales with a lifetime time horizon. The model applied a discount rate of 3.5% for costs and benefits. The cycle length was 4 weeks (28 days), and a half cycle correction was applied.

Model Inputs

Systematic literature reviews of the clinical and economic literature were used to inform the model (19). This was supplemented by further analysis of patient-level data from the eltrombopag clinical trial program. Due to the paucity of data in cITP, where data could not be identified through systematic review, inputs were taken from the romiplostim manufacturer submission or the international consensus report on the investigation and management of primary ITP (20-22).

Clinical Data

Response Rates: The response rate for eltrombopag was derived from patient-level data from RAISE and reflects the primary endpoint definition of response (i.e., patients achieving a platelet count of 50–400×10^9/L) at assessments during the 6-month treatment period (patients who received rescue treatments were regarded as non-responders for the duration of rescue treatment and until platelet counts fell to <50×10^9/L after ceasing rescue treatment) (12). An indirect treatment comparison (ITC) with romiplostim using this endpoint definition was not possible, as no such data were reported in the romiplostim trials.

In the romiplostim trials, a response was defined as a platelet count >50×10^9/L (15). Platelet responses that occurred within 8 weeks after receiving rescue treatment were not included in the efficacy analysis. Durable platelet response was defined as weekly platelet responses for ≥6 of the last 8 weeks of treatment. Patients who received rescue medication at any time during the study were not counted as having a durable response. Transient response was defined as ≥4 weekly platelet responses without a

durable platelet response from weeks 2 to 25. Overall platelet response was defined as durable plus transient rates of platelet response.

Post-hoc data analyses from RAISE were available, which were more comparable with the romiplostim trial endpoints of durable and overall responses (12). In these analyses, durable/sustained response was defined as a platelet count ≥50 and ≤400×10^9/L for ≥6 of the last 8 weeks of the 26-week treatment period. Patients receiving rescue medication at any time and those who prematurely withdrew from the study were considered to have not achieved a durable/sustained response. Transient response was defined as a platelet count response for ≥4 consecutive weeks during treatment and included all data up to the time of withdrawal for premature withdrawals. Overall response was defined as having either a durable/sustained response or a transient response (12).

Some important differences in the design of RAISE and the romiplostim trials suggest that the data available for the two drugs are not entirely comparable. However, the broad similarities in the patient populations provided a reasonable justification for conducting an adjusted ITC using these post-hoc analyses for use in a sensitivity analysis. The Bucher technique (23) was applied for the adjusted ITC. This method maintains the randomization from each trial and provides estimates of the treatment effect for eltrombopag versus romiplostim (e.g., odds ratios [OR]) and 95% confidence intervals [CIs]) (Table 2). Analyses were conducted separately for splenectomized and non-splenectomized patients. Results of the ITC of response rates suggested no statistically significant differences between the two TPO-RAs regarding overall or durable responses for either splenectomized or non-splenectomized patients, evidenced by wide CIs that cross one.

An ITC of bleeding events was also performed but was not used for the purpose of economic modeling. Due to the very small number of bleeding events, no significant differences were observed between eltrombopag and romiplostim, and point estimates had very wide CIs (data not shown). Differences in bleeding endpoint definitions also confounded this comparison. In order to inform long-term outcomes for this model, we estimated bleed rates conditional upon platelet level using data from RAISE and EXTEND as described below. It was assumed that these estimates were valid for both eltrombopag and romiplostim.

In the base case, the effectiveness of romiplostim was assumed to be the same as eltrombopag, and it was based on the response rates for eltrombopag observed in the RAISE trial. For non–TPO-RA treatments, only naïve comparisons were possible as no direct or comparative data with common control arms were available to perform an adjusted ITC. Weighted averages were taken from the systematic review and, where data were not stratified by splenectomy status, it was assumed that the proportion of splenectomized patients and the relative risk of response in splenectomized versus non-splenectomized patients was the same as for patients in RAISE.

Time to Response: The modeled time to response for eltrombopag was derived from RAISE data and reflects the time at which the proportion of patients responding to eltrombopag stabilizes (Table 3) (12). For romiplostim, the maximum time from treatment initiation to initial response is assumed to be 4 weeks, reflecting that seen in the Kuter et al. trials (15). Time to response for non–TPO-RAs was taken from the systematic review and was not differentiated for splenectomized versus non-splenectomized patients, as insufficient data were available to inform these estimates. To avoid creating a large number of tunnel states in the model, any time to response for the non-TPO-RAs >4 cycles (16 weeks) was truncated at 16 weeks.

Time on Treatment: Time on treatment for eltrombopag was based on treatment cessation data from RAISE and EXTEND, where time on treatment for patients randomized to eltrombopag and classified as responders was modeled as a survival variable. An adjusted parametric analysis was conducted to analyze the effect of prior splenectomy and to enable estimation of time on treatment beyond the combined duration of RAISE and EXTEND. The log-normal distribution provided the best statistical fit to the empirical data. Non-responders were assumed to experience the cost of TPO-RAs for one cycle only, after which it was assumed that response would be assessable and non-responders would stop treatment.

Because similar data were not available for romiplostim, time on treatment for romiplostim was assumed to be equal to that for eltrombopag. Time on treatment for non–TPO-RA treatments was taken from the clinical systematic review (19). In the absence of robust data and in order to avoid increasing model complexity, time on treatment was assumed to follow an exponential distribution for all non–TPO-RA

treatments.

Risk of Bleeding: Patients in responder and non-responder states faced a risk of day-case bleeds and of bleeds requiring hospitalization (19). Bleeding risks were estimated using patient-level data from the eltrombopag clinical trial program as the number of events experienced per unit time for patients with either platelet counts ≥50 or $<50\times10^9$/L (Appendix Table 1). Bleeding events not expected to be associated with any medical intervention were not included in the model. Given a lack of data, bleeding rates were assumed to double when patients entered the long-term non-responder state following their last treatment, based on assumptions made in the NICE appraisal of romiplostim (20). Bleeds requiring hospitalization were subdivided into intracranial hemorrhage, gastrointestinal, and other bleeds using individual patient data from RAISE/EXTEND (Appendix Table 2).

Mortality: ITP mortality was based on mortality rates associated with different ITP-related hospitalizations for severe bleeds (Appendix Table 3) (24). All-cause mortality was based on national statistics (25) and the average age and sex distribution were based on those observed in RAISE.

Risk of Rescue: The rate of rescue conditional upon platelet level (i.e., for patients in a responder or non-responder health state) was derived from RAISE/EXTEND, where the number of rescue events per unit time was estimated for patients with platelet levels ≥50 and $<50\times10^9$/L (Appendix Table 4). The proportions of each rescue type were also taken from RAISE and EXTEND (Appendix Table 5). It was assumed that these estimates were valid for both eltrombopag and romiplostim. This analysis of RAISE and EXTEND was restricted to countries with health care resources comparable to those in the UK.

AE Rates: AEs were grouped into serious AEs and other AEs. AE rates were taken from the manufacturer's submission of romiplostim, as minimal information was found through systematic review (Appendix Table 6) (21). AE rates for eltrombopag were assumed to be equal to those for romiplostim.

Utility Values

Utility values were mainly taken from a vignette study where health state descriptions were based on individual patient data collected via the ITP-patient assessment questionnaire (26). Time trade-off

techniques were used to elicit evaluations for these health states from 359 members of the UK general public. Disutilities associated with serious bleeds and AEs were obtained from the literature (Appendix Table 7) (27).

Costs

Drug acquisition costs were derived from British National Formulary 63 and reflect 2010/2011 pricing (accessed July 2012; no adjustment made) (Table 4) (28). The confidential discounts available to the NHS for romiplostim and eltrombopag through patient access schemes were also applied to these costs in order to reflect the true cost to the NHS. Eltrombopag and romiplostim doses used within the model were based on data from RAISE and the Kuter et al. trial (12, 15). To reflect dosing titration according to platelet response, doses were estimated for 4-week periods up to 23 weeks, beyond which the dose was assumed to be stable. Eltrombopag is available as a daily oral tablet and romiplostim as a weekly subcutaneous injection. Romiplostim vial wastage was incorporated into the model by calculating the number of vials each patient would require based on their baseline weight (the distribution of individuals' baseline weights was obtained from RAISE). Dosing for non–TPO-RA treatments was taken from either the international consensus report (22) or the manufacturer's submission for romiplostim (21), and administration costs were based on NHS reference costs (29). Based on available data, it was estimated that 72% of romiplostim patients in the UK would be able to self-administer these drugs at home and would therefore incur no administration costs (30). Note that this may not be the case for other jurisdictions. Health state costs comprised the costs of treating bleeding events and follow-up costs (Table 4).

Sensitivity Analyses

A range of deterministic sensitivity analyses were performed where all key model inputs were varied (Appendix Table 8). Probabilistic sensitivity analyses were conducted by simultaneously sampling from estimated probability distributions of model parameters (Appendix Table 9) to obtain 1,000 sets of model estimates.

RESULTS

Eltrombopag dominated romiplostim in both splenectomized and non-splenectomized patients in the probabilistic base case analyses (i.e., eltrombopag had 0.02 more quality-adjusted life-years [QALYs] and was less costly than romiplostim) (Table 5). In splenectomized patients, eltrombopag was associated with 0.02 more QALYs than romiplostim and was £88,904 less costly per patient over the patient's lifetime. In non-splenectomized patients, eltrombopag was associated with 0.02 more QALYs and was £40,261 less costly per patient.

Probabilistic sensitivity analysis results are presented on the cost-effectiveness planes in Figures 2A and 2C. Cost-effectiveness acceptability curves demonstrated that, at a cost-effectiveness threshold of £20,000/QALY, the probability that eltrombopag is cost-effective versus romiplostim was 99% and 92% in splenectomized and non-splenectomized patients, respectively (Figs. 2B and 2D).

This base-case finding of dominance was maintained in all of the deterministic sensitivity analyses performed with the exception of where the OR from the ITC of overall response was used to inform the relative efficacy of the TPO-RAs. In this analysis for splenectomized patients, eltrombopag was associated with 0.16 fewer QALYs than romiplostim and was £121,451 less costly per patient (Table 5). In non-splenectomized patients, eltrombopag was associated with 0.08 fewer QALYs and was £57,958 less costly per patient. This resulted in incremental cost-effectiveness ratios (ICERs) of £754,830/QALY and £724,475/QALY for eltrombopag versus romiplostim in splenectomized and non-splenectomized patients, respectively. These ICERs were situated in the southwest quadrant of the cost-effectiveness plane and were therefore interpreted differently from ICERs in the northeast quadrant, which is where most ICERs of new treatments fall (Appendix Figure 1A and 1C). For ease of interpretation, these figures can be considered the ICERs for romiplostim versus eltrombopag, where romiplostim was more effective yet more costly. The cost-effectiveness acceptability curves for the probabilistic analysis are shown in Appendix Figure 1B and 1D. The ITC analyses therefore support the base case analyses and finds eltrombopag to be cost-effective at a cost-effectiveness threshold of £20,000 per QALY.

DISCUSSION

There is a lack of evidence-based treatments available for cITP; however, the two TPO-RAs eltrombopag

and romiplostim represent a class of treatments supported by a relatively robust evidence base. The use of both TPO-RAs is supported by clinical trial programs that have demonstrated their long-term safety and efficacy in the treatment of patients with cITP (17, 31).

Our base-case results suggest that eltrombopag is a cost-effective alternative to romiplostim. This result was relatively insensitive to the range of deterministic sensitivity analyses performed and was primarily driven by the lower total drug costs associated with eltrombopag. Furthermore, eltrombopag is administered as a once-daily tablet, whereas romiplostim is administered as a weekly subcutaneous injection. For simplicity, we made no attempt to incorporate the benefits of an oral therapy into this analysis. However, oral availability may be associated with a utility gain as well as benefits in terms of convenience and pharmacy/nursing capacity compared with an injection.

A key assumption in our base case is that the two TPO-RAs have equivalent efficacy (i.e., a class effect exists). This assumption is consistent with clinical opinion (i.e., ITP guidelines do not distinguish between the two treatments). No head-to-head randomized trials were available to compare the two TPO-RAs. However, due to the presence of a common comparator and the availability of post-hoc analyses of RAISE, it was possible to conduct ITCs. A scenario analysis using results from the ITC of overall response allowed us to explore the impact of the uncertainty around the assumption of a class effect. Although performing ITCs is now a generally accepted method, these results should be interpreted with caution and in the context of the limitations and possible bias associated with them. There are several factors that increase the uncertainty of such an analysis in this particular case:

- Differences in the patient populations of RAISE versus the two Kuter et al. trials (15, 30) regarding ITP duration, previous use of ITP medications, and use of concomitant medications.

- Durable response was the primary endpoint of the romiplostim studies and a post-hoc analysis for eltrombopag. Overall response is the sum of “durable” and “transient” responses. Durable response was similarly defined in the romiplostim trials and the eltrombopag post-hoc analysis: a response in ≥6 of the last eight visits of the treatment period. However, the definition of “transient response” was different: a transient response in the romiplostim trials required a response at any four weekly visits

during the study, whereas the eltrombopag analysis required four consecutive weekly visits. In a disease where platelet counts fluctuate, four consecutive responses are more difficult to achieve, and this is likely to have biased the ITC against eltrombopag.

- While tapering or interruptions of concomitant ITP medications were not allowed during the last 12 weeks of the romiplostim study, physicians in RAISE were encouraged to reduce concomitant ITP medications once a stable eltrombopag dose was achieved. This was more likely to occur towards the end of the trial, when durable response was assessed in the post-hoc analysis. Platelet count fluctuations are expected as a result of tapering ITP medications, and this most likely negatively impacted the response estimates for eltrombopag.

- The number of durable and overall responders in the placebo arm of the romiplostim study was very low. As such, any ITC is very sensitive to small changes in this event rate.

- The Evidence Review Group (ERG) for the NICE appraisal of elrombopag felt that a Bayesian rather than a Bucher approach should have been used to conduct the ITC in the overall RAISE population. However, due to the small amount of data available this was not found to be feasible by the ERG when analyzing splenectomized and non-splenectomized patients separately (32); therefore, it was not used in the current work. We note that in the overall population alternative approaches applied to this data have led to outcomes consistent with the Bucher approach (33); therefore, we do not anticipate that this would have changed the overall outcome of the cost-effectiveness comparison.

Given the limitations and possible bias surrounding a comparison of the TPO-RAs, we assumed a class effect in the base case and used results from the ITC in a sensitivity analysis.

Where results from the ITC are used, eltrombopag is less effective but significantly less costly than romiplostim, with ICERs for eltrombopag versus romiplostim lying in the southwest quadrant of the cost-effectiveness plane. In such situations, ICERs for eltrombopag that lie above (rather than below) the cost-effectiveness threshold are considered to indicate cost-effectiveness (i.e., at a threshold of £20,000/QALY we want to observe at least £20,000 of savings per QALY lost). When the ITC is incorporated into the model, the resulting ICERs greatly exceed this threshold (i.e., eltrombopag offers savings of

>£100,000/QALY lost); therefore, eltrombopag is considered cost-effective. Results of this scenario analysis are reassuring for the decision maker given the uncertainty regarding the relative efficacy of eltrombopag and romiplostim.

Other major areas of uncertainty were identified by the NICE committee (19). Sensitivity analyses show that conclusions were not sensitive to rescue or bleeding rates, or the use of alternative utility data. We made the simplifying assumption that patients who experience an overall response sustain platelet levels $\geq 50 \times 10^9$/L and those who do not achieve response sustain platelet levels $<50 \times 10^9$/L. Realistically, platelet levels will fluctuate in both groups and we will have exaggerated the benefits of response (vs. non-response). As comparator response rates are equal in the base case, this will have limited impact on incremental costs and QALYs. In the sensitivity analysis using data from the ITC, the analysis will exaggerate the health benefits and reduced costs associated with response and thereby bias the results in favour of romiplostim. Patients receiving and responding to treatment with romiplostim were assumed to have a duration of treatment based on the empirical data from the eltrombopag trials. NICE considered this reasonable in the absence of other robust evidence (19); however, further information on treatment duration would improve the robustness of the analysis. Finally, NICE considered that lower dosing of romiplostim in responders and eltrombopag in practice, and lower administration costs for romiplostim, may reduce costs (19). However, data to model these scenarios were not available and the best available data were used in the context of the current model. Despite these concerns, the committee concluded that using their preferred assumptions gave ICERs for eltrombopag compared to romiplostim of more than £250,000 saved per QALY lost, and that eltrombopag was a cost-effective use of NHS resources.

Unfortunately, it is unlikely that additional efficacy data will become available to inform this decision problem. Given the low incidence of cITP, we suggest that it would be infeasible to recruit the estimated sample required to conduct a non-inferiority (>2,000 patients) or superiority randomized controlled trial (>3,000 patients) of romiplostim versus eltrombopag. The collection of observational data through the existing UK ITP registry may provide a useful source of information for future assessments of cITP treatments, particularly the long-term benefits of elevated platelet levels in a real-world setting. The current model compared the use of eltrombopag to romiplostim at the position in the treatment pathway in

which romiplostim is currently used. Further work is required to define optimal treatment sequences in cITP and, in particular, whether it may be cost-effective to use the new TPO-RAs in sequence. This economic evaluation demonstrates that eltrombopag provides patients and clinicians with a cost-effective, oral treatment option for a disease for which there are few evidence-based treatments available.

REFERENCES

1. Cooper N, Bussel J. The pathogenesis of immune thrombocytopaenic purpura. Br J Haematol 2006;133:364-74.
2. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.
3. Bennett D, Hodgson ME, Shukla A, Logie JW. Prevalence of diagnosed adult immune thrombocytopenia in the United Kingdom. Adv Ther 2011;28:1096-104.
4. Portielje JE, Westendorp RG, Kluin-Nelemans HC, Brand A. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood 2001;97:2549-54.
5. Mathias SD, Gao SK, Miller KL, et al. Impact of chronic Immune Thrombocytopenic Purpura (ITP) on health-related quality of life: a conceptual model starting with the patient perspective. Health Qual Life Outcomes 2008;6:13.
6. Thota S, Kistangari G, Daw H, Spiro T. Immune thrombocytopenia in adults: an update. Cleve Clin J Med 2012;79:641-50.
7. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207.
8. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med 2007;357:2237-47.
9. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:641-8.
10. Jenkins JM, Williams D, Deng Y, et al. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. Blood 2007;109:4739-41.
11. Nieto M, Calvo G, Hudson I, et al. The European Medicines Agency review of eltrombopag (Revolade) for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura: summary of the scientific assessment of the Committee for Medicinal Products for Human Use. Haematologica 2011;96:e33-40.

12. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 2011;377:393-402.
13. Saleh MN, Bussel JB, Cheng G, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood 2013;121:537-45.
14. Bussel J, Saleh MN, Wong RSM, et al. Update on the safety and efficacy of EXTENDed treatment with eltrombopag (EPAG) in adults with chronic immune thrombocytopenia (ITP) [abstract]. Blood 2013;122:2315.
15. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008;371:395-403.
16. Kuter DJ, Rummel M, Boccia R, et al. Romiplostim or standard of care in patients with immune thrombocytopenia. N Engl J Med 2010;363:1889-99.
17. Bussel JB, Kuter DJ, Pullarkat V, et al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood 2009;113:2161-71.
18. European Medicines Agency (EMA). Committee for Medicinal Products for Human Use Summary of Positive Opinion for Nplate. London, United Kingdom: European Medicines Agency (EMA), 2008.
19. National Institute for Health and Care Excellence (NICE). Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (review of technology appraisal 205). London, United Kingdom: National Institute for Health and Care Excellence, 2013.
20. National Institute for Health and Care Excellence (NICE). Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. London, United Kingdom: National Institute for Health and Care Excellence, 2011; last modified May 2014.
21. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal (STA): Romiplostim for the Treatment of Chronic Immune or Idiopathic Thrombocytopenic Purpura (ITP); Interim Submission of Evidence by Manufacturer: Amgen Inc. London, United Kingdom: National Institute for Health and Care Excellence, 2008.

22. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115:168-86.
23. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683-91.
24. Danese MD, Lindquist K, Gleeson M, et al. Cost and mortality associated with hospitalizations in patients with immune thrombocytopenic purpura. Am J Hematol 2009;84:631-5.
25. National Life Tables 2007–2009. Available from: http://www.ons.gov.uk/ons/publications/re-reference-tables.html?edition=tcm%3A77-61850. [Accessed September 8, 2014].
26. Szende A, Brazier J, Schaefer C, et al. Measurement of utility values in the UK for health states related to immune thrombocytopenic purpura. Curr Med Res Opin 2010;26:1893-903.
27. Leontiadis GI, Sreedharan A, Dorward S, et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess 2007;11:iii-iv, 1-164.
28. British National Formulary 63. 2012.
29. National Health Service (NHS) Reference Costs 2010–2011 Publication. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/215297/dh_131160.pdf. [Accessed September 8, 2014].
30. Kuter DJ, Bussel JB, Newland A, et al. Long-term efficacy and safety of romiplostim treatment of adult patients with chronic immune thrombocytopenia (ITP): final report from an open-label extension study [abstract]. Blood 2010;116:68.
31. Kuter DJ, Bussel JB, Newland A, et al. Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. Br J Haematol 2013;161:411-23.
32. Cummins E, Fielding S, Scott N, et al. Eltrombopag for the treatment of chronic immune thrombocytopenic purpura. Aberdeen, Scotland: Institute of Applied Health Sciences, University of Aberdeen, 2012. Available from: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0004/82606/ERGReport-12-07-01.pdf. [Accessed February 24, 2016].

33. Cooper KL, Fitzgerald P, Dillingham K, et al. Romiplostim and eltrombopag for immune thrombocytopenia: methods for indirect comparison. Int J Technol Assess Health Care. 2012;28:249-58.

FIGURE LEGENDS

Figure 1. Model structure. LT, long term; NR, non-responder; Resp, responder; W, week.

Figure 2. A) Probabilistic sensitivity analysis (1,000 simulations) and B) cost-effectiveness acceptability curves for splenectomized patients, and C) probabilistic sensitivity analysis (1,000 simulations) and D) cost-effectiveness acceptability curves for non-splenectomized patients. QALYs, quality-adjusted life-years.

Figure 1

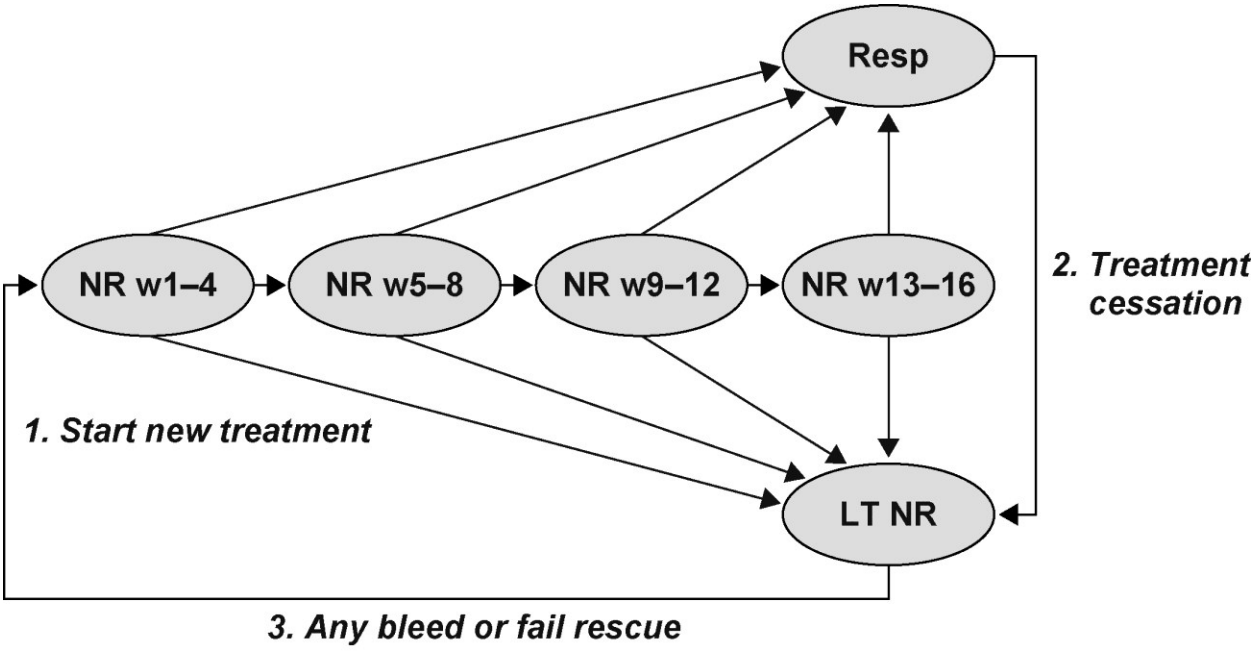


Figure 2

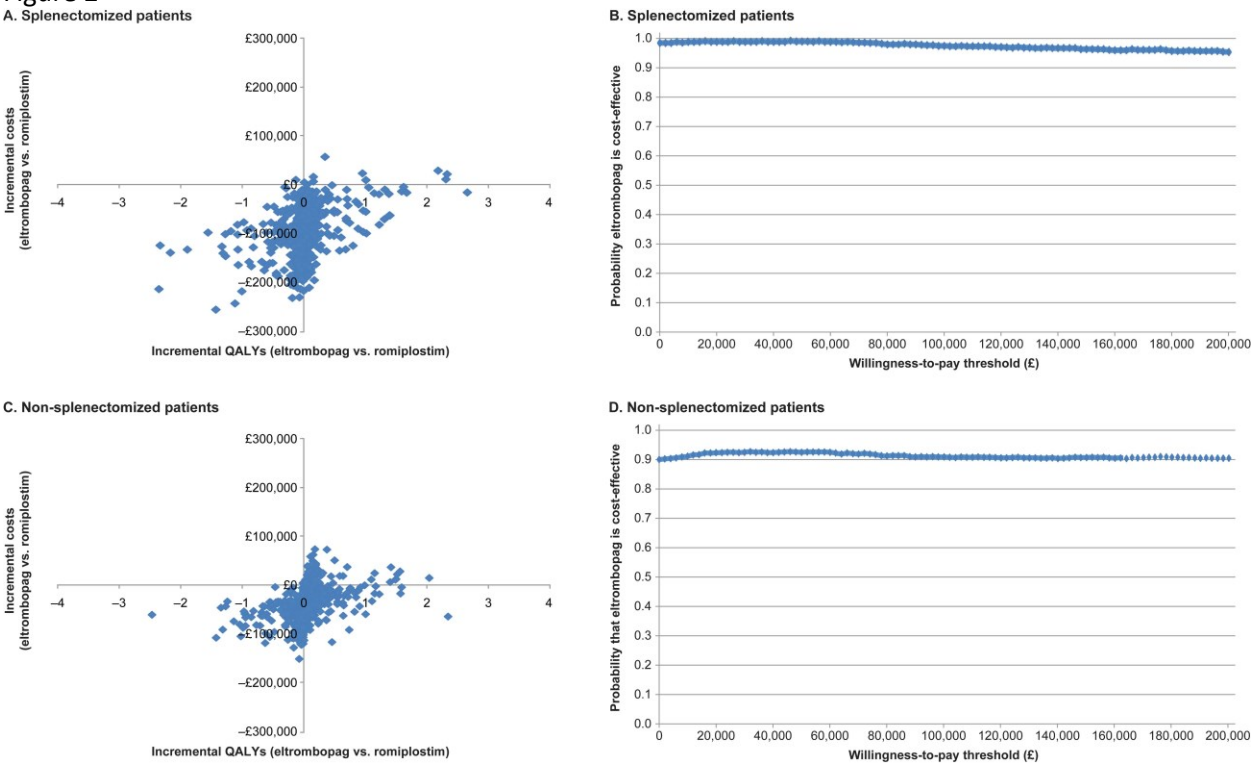

A. Splenectomized patients
Incremental costs (eltrombopag vs. romiplostim)
£300,000
£200,000
£100,000
£0
–£100,000
–£200,000
–£300,000
–4
–3
–2
–1
0
1
2
3
4
Incremental QALYs (eltrombopag vs. romiplostim)
B. Splenectomized patients
Probability eltrombopag is cost-effective
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000
Willingness-to-pay threshold (£)
C. Non-splenectomized patients
Incremental costs (eltrombopag vs. romiplostim)
£300,000
£200,000
£100,000
£0
–£100,000
–£200,000
–£300,000
–4
–3
–2
–1
0
1
2
3
4
Incremental QALYs (eltrombopag vs. romiplostim)
D. Non-splenectomized patients
Probability that eltrombopag is cost-effective
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
160,000
180,000
200,000
Willingness-to-pay threshold (£)

Table 1. Number of previous treatments for chronic immune thrombocytopenia among participants in the RAISE Study (12).

	Placebo (n=62)	Eltrombopag (n=135)
Two or more	50 (81%)	105 (78%)
Three or more	32 (52%)	75 (56%)
Four or more	20 (32%)	51 (38%)
Five or more	11 (18%)	35 (26%)

Table 2. ITC of overall and durable responses.

	Eltrombopag vs. placebo, OR (95% CI)	Romiplostim vs. placebo, OR (95% CI)	ITC of eltrombopag vs. romiplostim, OR (95% CI)
Durable/sustained response			
Splenectomized patients	13.33 (1.66–107.43)	26.77 (1.52–472.41)	0.50 (0.01–17.32)
Non-splenectomized patients	12.97 (3.72–45.26)	31.25 (3.81–256.24)	0.41 (0.04–4.80)
Overall response			
Splenectomized patients	14.25 (2.98–68.02)	151.63 (8.39–2,741.84)	0.09 (0.00–2.52)
Non-splenectomized patients	14.83 (5.53–39.76)	43.20 (9.27–201.33)	0.34 (0.06–2.14)

CI, confidence interval; ITC, indirect treatment comparison; OR, odds ratio.

Table 3. Efficacy parameters.

Drug	Response proportion		Time to response	Duration of response (mean)
	Splenectomized	Non-splenectomized		
Eltrombopag	76%	80%	2 weeks (15 days)	Log-normal distribution assigned
Romiplostim	76%	80%	4 weeks (28 days)	Equivalent to eltrombopag
Rituximab	57%	60%	3.5 weeks (24.4 days)	24.6 months (748.4 days)
Azathioprine	44%	46%	16 weeks (112 days)	91 months (2,769.8 days)
Mycophenolate mofetil	51%	54%	5 weeks (35 days)	1.7 months (50.5 days)
Cyclosporine	41%	43%	3.5 weeks (24.5 days)	28.6 months (870.5 days)
Dapsone	44%	46%	5.1 weeks (35.5 days)	25.8 months (785.6 days)
Danazol	35%	37%	18 weeks (126 days)	145 months (4,413.3 days)
Cyclophosphamide	82%	87%	8.5 weeks (59.5 days)	41.7 months (1,268.8 days)
Vinca alkaloids	56%	59%	2.0 weeks (13.7 days)	41.7 months (1,268.8 days)
Rescue – IVIg	80%	84%	3.5 days (assumed instantaneous in	17.2 days (assumed 1 month)

			model)	
Rescue – Anti-D	41%	43%	4.3 days (assumed instantaneous in model)	42.7 days (assumed 1 month)
Rescue – IV corticosteroid	40%	42%	7.04 days (assumed instantaneous in model)	Assumed 1 month
Rescue – platelet transfusion	41%	43%	Assumed instantaneous in model	Assumed 1 month

IV, intravenous; IVIg, intravenous immunoglobulin.

Table 4. Costs used in the economic model.

Drug	Acquisition cost	Size (mg)	Administration cost	NHS reference costs
	BNF 63 (28)		HRG code	2010/2011
Eltrombopag*	£770.00	700 (28 x 25)	N/A	N/A
Romiplostim*	£482.00	0.25	SB12Z	£204.81
Azathioprine	£5.04	1,400		
Mycophenolate mofetil	£35.00	25,000		
Cyclosporine	£13.80	750	N/A	N/A
Dapsone	£54.56	2,800		
Danazol	£16.38	6,000		
Cyclophosphamide	£20.20	5,000		
Vincristine	£13.47	1	SB12Z	£204.81
Vinblastine	£13.09	10	SB12Z	£204.81
Rescue – IVIg	£45.00	1,000	XD34Z	£1,235.34
Rescue – Anti-D	£46.50	0.3	XD34Z	£1,235.34
Rescue – IV corticosteroid	£5.73	25	SB14Z	£330.59
Cost of treating bleeds				
Bleed type	HRG code		NHS reference costs 2010/2011	
Day-case bleed	SA08F Other hematological or splenic disorders without CC – day case		£302.81	
Gastrointestinal bleed	FZ38 Gastrointestinal hemorrhage, unspecified		Inpatient £1,553 (weighted average over HRG codes FZ38D, FZ38E, and FZ38F)	
Intracranial hemorrhage	Intracranial hemorrhage (non-traumatic), unspecified		Inpatient £3,451 (weighted average over HRG codes AA23A and AA23B)	
Other bleed requiring	Assumed equal to FZ38		Inpatient £1,553	

hospitalization

Follow-up costs (applied every 4 weeks to all patients)		
	HRG code	NHS reference costs 2010/2011
Hematologist consultation	303 Clinical hematology, consultant led: First attendance non-admitted face to face	£147.53
Blood test	DAP823 Hematology	£3.00
Biochemistry	DAP841 Biochemistry	£1.00

*Discounts were applied.

BNF, British National Formulary; CC, complications and comorbidities; HRG, Health Resource Group; IV, intravenous; IVIg, intravenous immunoglobulin; N/A, not available; NHS, National Health Service.

Table 5. Cost-effectiveness results for the base-case (probabilistic) and deterministic sensitivity analysis incorporating indirect efficacy estimates.

Drug	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICERs (£/QALY) vs. romiplostim
Base case (probabilistic)					
Splenectomized					
Eltrombopag	£322,900	14.83			Referent
Romiplostim	£411,804	14.81	£88,904	−0.02	Dominanted
Non-splenectomized					
Eltrombopag	£236,339	15.33			Referent
Romiplostim	£276,600	15.31	£40,261	−0.02	Dominanted
Incorporating indirect efficacy estimates (probabilistic)					
Splenectomized					
Eltrombopag	£323,209	14.79			Referent
Romiplostim	£444,660	14.95	£121,451	0.16	£754,830
Non-splenectomized					
Eltrombopag	£231,215	15.34			Referent
Romiplostim	£289,173	15.42	£57,958	0.08	£724,475

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SW, southwest

References

1. Cooper N, Bussel J. The pathogenesis of immune thrombocytopaenic purpura. British journal of haematology. 2006; 133: 364-74.
2. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009; 113: 2386-93.
3. Bennett D, Hodgson ME, Shukla A, et al. Prevalence of diagnosed adult immune thrombocytopenia in the United Kingdom. Advances in therapy. 2011; 28: 1096-104.
4. Portielje JE, Westendorp RG, Kluin-Nelemans HC, et al. Morbidity and mortality in adults with idiopathic thrombocytopenic purpura. Blood. 2001; 97: 2549-54.
5. Mathias SD, Gao SK, Miller KL, et al. Impact of chronic Immune Thrombocytopenic Purpura (ITP) on health-related quality of life: a conceptual model starting with the patient perspective. Health and quality of life outcomes. 2008; 6: 13.
6. Thota S, Kistangari G, Daw H, et al. Immune thrombocytopenia in adults: an update. Cleveland Clinic journal of medicine. 2012; 79: 641-50.
7. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011; 117: 4190-207.
8. Bussel JB, Cheng G, Saleh MN, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. The New England journal of medicine. 2007; 357: 2237-47.
9. Bussel JB, Provan D, Shamsi T, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomised, double-blind, placebo-controlled trial. Lancet. 2009; 373: 641-8.
10. Jenkins JM, Williams D, Deng Y, et al. Phase 1 clinical study of eltrombopag, an oral, nonpeptide thrombopoietin receptor agonist. Blood. 2007; 109: 4739-41.
11. Nieto M, Calvo G, Hudson I, et al. The European Medicines Agency review of eltrombopag (Revolade) for the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura: summary of the scientific assessment of the Committee for Medicinal Products for Human Use. Haematologica. 2011; 96: e33-40.
12. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet. 2011; 377: 393-402.
13. Saleh MN, Bussel JB, Cheng G, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood. 2013; 121: 537-45.
14. Bussel J, Saleh MN, Wong RSM, et al. Update On The Safety and Efficacy Of EXTENDed Treatment With Eltrombopag (EPAG) In Adults With Chronic Immune Thrombocytopenia (ITP). Blood. 2013; 122: Abstract 2315.
15. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet. 2008; 371: 395-403.
16. Kuter DJ, Rummel M, Boccia R, et al. Romiplostim or standard of care in patients with immune thrombocytopenia. The New England journal of medicine. 2010; 363: 1889-99.
17. Bussel JB, Kuter DJ, Pullarkat V, et al. Safety and efficacy of long-term treatment with romiplostim in thrombocytopenic patients with chronic ITP. Blood. 2009; 113: 2161-71.
18. EMA. Committee for Medicinal Products for Human Use Summary of Positive Opinion for Nplate. London, United Kingdom: European Medicines Agency (EMA), 2008.
19. NICE. Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (review of technology appraisal 205). London, United Kingdom: National Institute for Health and Clinical Excellence, 2013.
20. NICE. Romiplostim for the treatment of chronic immune (idiopathic) thrombocytopenic purpura. London, United Kingdom: National Institute for Health and Clinical Excellence, 2011.
21. NICE. Romiplostim for the Treatment of Chronic Immune or Idiopathic Thrombocytopenic Purpura (ITP). London, United Kingdom: National Institute for Health and Clinical Excellence, 2008.
22. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010; 115: 168-86.
23. Bucher HC, Guyatt GH, Griffith LE, et al. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. Journal of clinical epidemiology. 1997; 50: 683-91.

24. Danese MD, Lindquist K, Gleeson M, et al. Cost and mortality associated with hospitalizations in patients with immune thrombocytopenic purpura. American journal of hematology. 2009; 84: 631-5.
25. National Life Tables 2007-2009. Newport, South Wales, UK: Office for National Statistics, 2009.
26. Szende A, Brazier J, Schaefer C, et al. Measurement of utility values in the UK for health states related to immune thrombocytopenic purpura. Current medical research and opinion. 2010; 26: 1893-903.
27. Leontiadis GI, Sreedharan A, Dorward S, et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health technology assessment. 2007; 11: iii-iv, 1-164.
28. Kuznik A, Lamorde M, Hermans S, et al. Evaluating the cost-effectiveness of combination antiretroviral therapy for the prevention of mother-to-child transmission of HIV in Uganda. Bulletin of the World Health Organization. 2012; 90: 595-603.
29. Shah M, Johns B, Abimiku A, et al. Cost-effectiveness of new WHO recommendations for prevention of mother-to-child transmission of HIV in a resource-limited setting. AIDS. 2011; 25: 1093-102.
30. Kuter DJ, Bussel JB, Newland A, et al. Long-Term Efficacy and Safety of Romiplostim Treatment of Adult Patients with Chronic Immune Thrombocytopenia (ITP): Final Report from an Open-Label Extension Study. Blood. 2010; 116: Abstract 68.
31. Kuter DJ, Bussel JB, Newland A, et al. Long-term treatment with romiplostim in patients with chronic immune thrombocytopenia: safety and efficacy. British journal of haematology. 2013; 161: 411-23.
32. Cummins E, Fielding S, Scott N, et al. Eltrombopag for the treatment of chronic immune thrombocytopenic purpura. Aberdeen, Scotland: Institute of Applied Health Sciences, University of Aberdeen, 2012.
33. Cooper KL, Fitzgerald P, Dillingham K, et al. Romiplostim and eltrombopag for immune thrombocytopenia: methods for indirect comparison. International journal of technology assessment in health care. 2012; 28: 249-58.

SUPPLEMENTAL MATERIALS

Differences from the National Institute for Health and Care Excellence (NICE) Submission

Results presented in this manuscript differ from the base case in the manufacturer's submission to NICE [1]. **The base case analysis in the original NICE submission used a significant proportion of data from TA221 to ensure consistent decision-making between appraisals. In this manuscript the "alternative analysis" presented in the manufacturer's submission to NICE forms the base case.** This alternative analysis was considered to be more appropriate by the Evidence Review Group (ERG) and by the NICE committee, who considered this to be "*the most valid analysis because the modelling applied data derived directly from the pivotal trials of eltrombopag and the manufacturer's own systematic review*". In addition, the base case analysis in the NICE submission was based on deterministic analyses, whereas those in our manuscript are based on probabilistic analyses, in line with methodological best practice.

Probability of Receiving Each Treatment in the Treatment Pathway

The probability of receiving each drug, based on the National Institute for Health and Care Excellence (NICE) 2008 submission for romiplostim, was 59% for azathioprine, 37% for mycophenolate mofetil, 4% for cyclosporine, 7% for danazol, 48% for dapsone, 2% for cyclophosphamide, and 5% for vinca alkaloids [2].

Appendix Table 1. Bleed rates conditional upon platelet response.

Platelet count and hospital admission classification	Data from RAISE/EXTEND [3, 4]	
	Splenectomized	Non-splenectomized
Platelets ≥50×10^9/L – inpatient*	0.002	0.002
Platelets ≥50×10^9/L – day case	0.086	0.028
Platelets <50×10^9/L – inpatient*	0.008	0.008
Platelets <50×10^9/L – day case	0.341	0.214
Source	IPD analysis of RAISE/EXTEND, rate per 4-week cycle	

IPD, individual patient data.

* Due to the relatively low number of inpatient bleed occurrences, data were pooled across splenectomized and non-splenectomized patients.

Appendix Table 2. Distribution of bleed types among bleeds requiring hospitalization.*

Bleed type requiring hospitalization	Platelets <50×10^9/L, Proportion of all bleeds requiring hospitalization	Platelets ≥50×10^9/L, Proportion of all bleeds requiring hospitalization
Other bleed (coagulation disorder)	0.63	0.71
GI hemorrhage (GI bleeding)	0.19	0.29
Intracranial hemorrhage	0.19	0.00

GI, gastrointestinal; IPD, individual patient data.

* IPD analysis of RAISE and EXTEND [3, 4]; includes splenectomized and non-splenectomized patients.

Appendix Table 3. Proportion of deaths among patients with ITP-related hospitalization for severe bleed [5].

Discharge condition	Mortality rate, % (95% CI)
Other bleed (coagulation disorder)	1.7 (1.4–2.0)
GI hemorrhage (GI bleeding)	4.6 (2.7–6.4)
Intracranial hemorrhage	13.2 (9.8–16.6)

CI, confidence interval; GI, gastrointestinal; ITP, immune thrombocytopenia.

Appendix Table 4. Rates of rescue conditional on platelet response estimated from RAISE/EXTEND IPD.

	Splenectomized	Non-splenectomized
Platelets ≥50×10^9/L	0.05	0.01
Platelets <50×10^9/L	0.32	0.14
Source	IPD analysis of RAISE/EXTEND [3,4], rate per 4-week cycle	

IPD, individual patient data.

Appendix Table 5. Distribution of rescue types among patients requiring rescue.

	Scenario 1			
	Platelet count <50×10^9/L		Platelet count ≥50×10^9/L	
Rescue medication	Splenectomized	Non-splenectomized	Splenectomized	Non-splenectomized
IVIg	0.51	0.55	0.31	0.50
Anti-D	0.02*	0.18	0.00	0.14
IV steroid	0.11	0.07	0.14	0.36
Platelet transfusion	0.36	0.20	0.55	0.00
Source	RAISE/EXTEND [3,4] IPD analysis			

IPD, individual patient data; IV, intravenous; IVIg, intravenous immunoglobulin.

* The very small amount of anti-D use observed in splenectomized patients in the IPD was retained in the model; however, anti-D is not recommended for use in splenectomized patients [6, 7].

Appendix Table 6. 4-week probabilities of adverse events [2].

Drug	Event probability*	
	Serious AEs	Other AEs
Eltrombopag	3%†	31%†
Romiplostim	3%	31%
Rituximab	3%	0%
Azathioprine	15%	24%
Mycophenolate mofetil	15%	24%
Cyclosporine	15%	24%
Dapsone	11%	24%
Danazol	16%	35%
Cyclophosphamide	21%	30%
Vinca alkaloids	21%	30%
Rescue – IVIg	2%	0%
Rescue – Anti-D	3%	0%
Rescue – IV corticosteroid	3%	70%

AE, adverse event; IV, intravenous; IVIg, intravenous immunoglobulin.

* Mid-point used where range reported.

† Assumed to be the same as romiplostim, as there was no appreciable difference in safety between thrombopoietin-receptor agonists. Note: Platelet transfusions were assumed to be associated with no risk of “other” AEs and a 3% risk of “serious” AEs.

Appendix Table 7. Base-case utilities.

Health state	Mean	Standard error	Source
No bleed, sufficient platelets	0.863	0.0079	Szende et al 2010 [8]
Bleed, sufficient platelets	0.734	0.0100	
No bleed, low platelets	0.841	0.0100	
Bleed, low platelets	0.732	0.0100	
Intracranial hemorrhage (2–6 months)*	0.038	0.0243	
Corticosteroid treatment AE	0.758	0.0106	
Gastrointestinal bleed*	0.450	0.0561	Leontiadis et al 2007 [9]
Other bleed requiring inpatient treatment*	0.450	0.0561	Assumption
Four-week disutility associated with SAEs (associated with eltrombopag, romiplostim, and rituximab)†	0.100	0.025	
Four-week disutility associated with SAEs (associated with all other non-rescue treatments)	0.400	0.100	NICE TA221 [2]
Four-week disutility associated with SAEs (associated with rescue treatments)	0.10	0.025	
Four-week disutility associated with other AEs	0.10	0.025	

AEs, adverse events; SAEs, serious adverse events.

* Intracranial hemorrhage was assumed to impact utility for 4 months, and gastrointestinal bleeds and other bleeds were assumed to impact utility for one cycle (4 weeks).

† All AEs were assumed to last 4 weeks.

Appendix Table 8. Deterministic sensitivity analyses.

Deterministic sensitivity analyses	
Treatment pathway	TPO-RA received prior to rituximab
	TPO-RA as last active treatment in pathway
Response rates [3]	OR of 1.0 for TPO-RA comparison, baseline overall response as per RAISE post-hoc analysis
	OR taken from ITC, applied to baseline overall response as per RAISE post-hoc analysis
Time on treatment	Time on treatment for responders, log-logistic
	Time on treatment for responders, gamma
	Time on treatment for all patients, Gompertz
	Time on treatment for all patients, log-logistic
	Time on treatment for all patients, Weibull
Mortality	Mortality modeled via platelet level rather than bleeds
Rescue rates [2–4]	RAISE/EXTEND rate −25%
	Midpoint RAISE/EXTEND and TA221
	TA221
	TA221 +25%
Bleeding rates [2–4]	RAISE/EXTEND rate –25%
	Midpoint RAISE/EXTEND and TA221
	TA221
	TA221 +25%
Bleed risk in final non-responder state	Same as other non-responder states
Utilities	SF-6D data from the RAISE/EXTEND clinical trial program*
Costs	All patients receive romiplostim at outpatient visit
	No price discount for eltrombopag
	Romiplostim dose from Bussel et al 2009 extension trial [10]

Decision-maker parameters	Discount rate = 0%
	Discount rate = 6%
	Time horizon of 6 months
	Time horizon of 5 years
	Time horizon of 10 years
	Time horizon of 20 years

ITC, indirect treatment comparison; OR, odds ratio; SF-6D, six-dimensional health state short form; TPO-RA, thrombopoietin-receptor agonist.

* SF-36 (36-item Short-Form Health Survey) assessments pooled from RAISE [3] and EXTEND [4] mapped to the SF-6D are shown in Appendix Table 11.

Appendix Table 9. Distributions used for probabilistic sensitivity analysis.

Parameter	Distribution, parameterization
Probability of receiving each treatment	Beta, parameterized using parameter estimates from TA221 [2]
Response rates	Eltrombopag response: beta, event rates and sample sizes obtained from RAISE [3] IPD. For OR comparing romiplostim and eltrombopag, SE of log OR = 1.0 to reflect uncertainty regarding relative efficacy of treatments Non–TPO-RA: beta distribution, parameters taken from appropriate study
Time to response	Gamma, assume SE = 0.25*mean
Time on treatment	TPO-RA: multivariate normal distribution assumed for parameters of parametric distributions, covariance matrix obtained from survival analysis of RAISE/EXTEND IPD Non–TPO-RA: gamma, assume SE = 0.25*mean
Rescue rates	Gamma, assume variance equal to mean
Distribution of rescue types	Dirichlet taken directly from IPD for RAISE/EXTEND
Bleed rates	Gamma, assume variance equal to mean
Proportion of patients experiencing each bleed type	Dirichlet, taken directly from IPD for RAISE/EXTEND
Rates of mortality conditional upon bleed	Beta: α and β derived from events and sample size in Danese et al 2009 [5]
Utilities – health states and bleeds	Log-normal distribution use to model decrement from full health, parameterized using mean and SEs from Szende et al 2010 [8] and Leontiadis et al 2007 [9]
Adverse event rates	Beta: parameters obtained from TA221 [2]
Adverse event disutilities	Log-normal distribution use to model decrement, SE assumed equal to

	0.25*mean
Eltrombopag and romiplostim mean doses	Log-normal distribution, mean and SEs available from RAISE/EXTEND IPD for eltrombopag, and from Kuter et al 2008 [11] and Bussel et al 2009 [10] for romiplostim
Proportion of patients receiving romiplostim as home administration	Beta: α and β derived from events and sample size in Kuter et al 2010 [12]
Cost of bleeds, long-term follow-up, and treatment administration	Gamma used for unit costs, SE assumed equal to 0.25*mean. Dirichlet used for distribution of activity, directly parameterized using NHS reference cost activity rates

IPD, individual patient data; NHS, National Health Service; OR, odds ratio; SE, standard error; TPO-RA, thrombopoietin-receptor agonist.

Appendix Table 10. SF-6D values.*

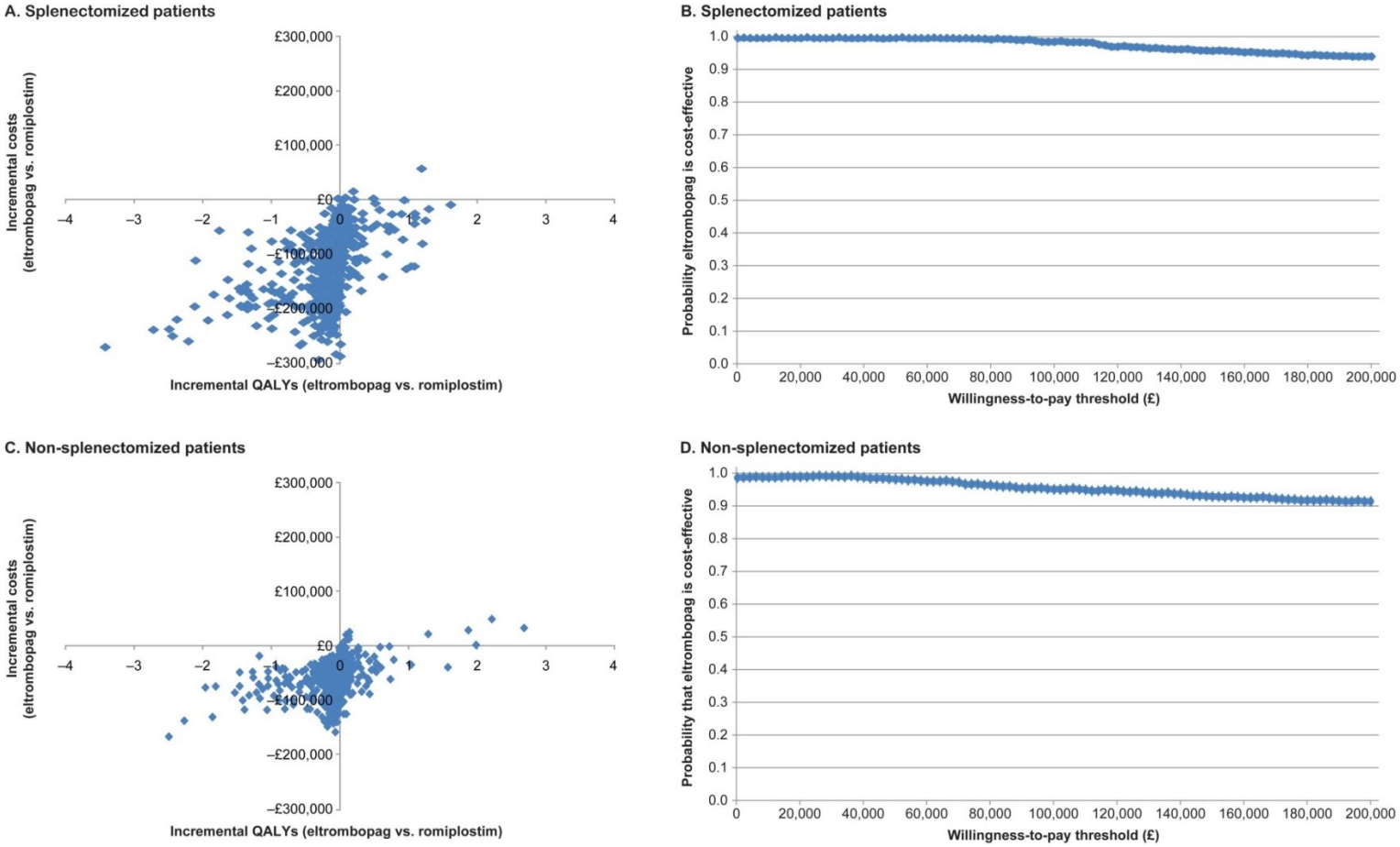
Health state	Splenectomized	Non-splenectomized
No bleed, sufficient platelets	0.737	0.761
Bleed, sufficient platelets	0.693	0.761
No bleed, low platelets	0.712	0.738
Bleed, low platelets	0.666	0.738

SF-6D, six-dimensional health state short form.

* Assessments from the 36-item Short-Form Health Survey (SF-36) pooled from RAISE and EXTEND.

Values used that were identical to base case are not shown.

Appendix Figure 1. A) Probabilistic sensitivity analysis (1,000 simulations) and B) cost-effectiveness acceptability curves for splenectomized patients, and C) probabilistic sensitivity analysis (1,000 simulations) and D) cost-effectiveness acceptability curves for non-splenectomized patients. QALYs, quality-adjusted life-years. Data based on indirect treatment comparison, probabilistic analysis.



REFERENCES

1. National Institute for Health and Care Excellence (NICE). Eltrombopag for treating chronic immune (idiopathic) thrombocytopenic purpura (review of technology appraisal 205). London: United Kingdom; National Institute for Health and Care Excellence (NICE), 2013.
2. National Institute for Health and Care Excellence (NICE). Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura (ITP). London: United Kingdom; National Institute for Health and Care Excellence (NICE), 2008.
3. Cheng G, Saleh MN, Marcher C, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomised, phase 3 study. Lancet 2011;377:393–402.
4. Saleh MN, Bussel JB, Cheng G, et al. Safety and efficacy of eltrombopag for treatment of chronic immune thrombocytopenia: results of the long-term, open-label EXTEND study. Blood 2013;121:537–45.
5. Danese MD, Lindquist K, Gleeson M, et al. Cost and mortality associated with hospitalizations in patients with immune thrombocytopenic purpura. Am J Hematol 2009;84:631–5.
6. Thota S, Kistangari G, Daw H, et al. Immune thrombocytopenia in adults: an update. Cleve Clin J Med 2012;79:641–50.
7. European Medicines Agency (EMA). Guidelines on the Clinical Development of Medicinal Products Intended for the Treatment of Chronic Primary Immune Thrombocytopenia. London: United Kingdom; European Medicines Agency (EMA), 2014.
8. Szende A, Brazier J, Schaefer C, et al. Measurement of utility values in the UK for health states related to immune thrombocytopenic purpura. Curr Med Res Opin 2010;26:1893–903.
9. Leontiadis GI, Sreedharan A, Dorward S, et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess 2007;11:iii-iv,1–164.
10. Bussel JB, Kuter DJ, Newland A, et al. Long-term efficacy and safety of romiplostim for the treatment of patients with chronic immune thrombocytopenia (ITP): 5-year update from an open-label extension study [abstract]. Blood 2009;114:2423.

11. Kuter DJ, Bussel JB, Lyons RM, et al. Efficacy of romiplostim in patients with chronic immune thrombocytopenic purpura: a double-blind randomised controlled trial. Lancet 2008;371:395–403.

12. Kuter DJ, Bussel JB, Newland A, et al. Long-term efficacy and safety of romiplostim treatment of adult patients with chronic immune thrombocytopenia (ITP): final report from an open-label extension study [abstract]. Blood 2010;116:68.